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# Body-fat indicators and kidney function decline in older post-myocardial infarction patients: The Alpha Omega Cohort Study

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## Abstract

**Background:** Obesity increases risk of hypertension and diabetes, the leading causes of end-stage renal disease. The effect of obesity on kidney function decline in stable post-myocardial infarction patients is poorly documented. This relation was investigated in a large cohort of older post-myocardial infarction patients.

**Design:** Data were analysed from 2410 post-myocardial infarction patients in the Alpha Omega Trial, aged 60–80 years receiving optimal pharmacotherapy treatment (79% men, 18% diabetes).

**Methods:** Cystatin C based estimated glomerular filtration rate (eGFR<sub>cysC</sub>) was calculated at baseline and after 41 months, using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Obesity was defined as body mass index  $\geq 30$  kg/m<sup>2</sup> and high waist circumference as  $\geq 102$  and  $\geq 88$  cm for men and women. The relation between body mass index, waist circumference and annual eGFR<sub>cysC</sub> decline was evaluated by linear regression.

**Results:** At baseline, mean (standard deviation) eGFR<sub>cysC</sub> was 81.5 (19.6) ml/min/1.73 m<sup>2</sup>, 23% of all patients were obese. After multivariable adjustment, the annual mean (95% confidence interval) eGFR<sub>cysC</sub> decline in men and women was  $-1.45$  ( $-1.59$  to  $-1.31$ ) and  $-0.92$  ( $-1.20$  to  $-0.63$ ) ml/min/1.73 m<sup>2</sup>, respectively ( $p = 0.001$ ). Obese versus non-obese patients and patients with high versus normal waist circumference experienced greater annual eGFR<sub>cysC</sub> decline. Men and women showed an additional annual eGFR<sub>cysC</sub> decline of  $-0.35$  ( $-0.56$  to  $-0.14$ ) and  $-0.21$  ( $-0.55$  to  $0.14$ ) ml/min/1.73 m<sup>2</sup> per 5 kg/m<sup>2</sup> body mass index increment ( $p$  for interaction 0.3).

**Conclusions:** High compared to normal body mass index or waist circumference were associated with more rapid kidney function decline in older stable post-myocardial infarction patients receiving optimal drug therapy.

## Keywords

Obesity, kidney function, risk factors, cardiovascular disease

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## Introduction

The prevalence of obesity has increased to epidemic proportions and is ranked globally in the top five risk factors for death.<sup>1</sup> Obesity, defined as a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>, is associated with an increased risk of cardiovascular morbidity and mortality, as well as accelerated kidney function decline.<sup>1–3</sup> Impaired kidney function itself is a robust and independent risk factor for cardiovascular morbidity and mortality.<sup>4</sup> The annual rate of kidney function decline in post-myocardial infarction (post-MI) patients is more than double that of the general population.<sup>5,6</sup>

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Obesity may promote kidney damage through both haemodynamic and hormonal effects. The deleterious effects of obesity on the kidney are, in part, mediated by cardiovascular risk factors such as diabetes mellitus, hypertension and dyslipidaemia.<sup>1</sup> Additionally, accumulation of visceral fat can increase production of inflammatory mediators by adipocytes, contributing to glomerular and interstitial fibrosis.<sup>7</sup> Furthermore, obesity is associated with an increase in the single-nephron glomerular filtration rate, which may lead to glomerulosclerosis and subsequent progressive loss of kidney function.<sup>8</sup>

Several studies have suggested a paradoxical effect of obesity in individuals with pre-existing chronic illness, such as chronic kidney disease, showing that obesity is associated with improved survival or kidney function.<sup>9,10</sup> This 'obesity paradox' challenges current guidelines, which advise weight reduction towards an ideal BMI of 20–25 kg/m<sup>2</sup>.<sup>11</sup>

The aim of this study was to assess the association between obesity and the rate of kidney function decline in older post-MI patients receiving state-of-the-art drug treatment, separately for men and women, who differ in body composition. These results might inform care guidelines for post-MI patients.

## Methods

### Study design

This is a secondary analysis of the prospective Alpha Omega Cohort Study (ClinicalTrials.gov no. NCT03192410). The cohort consists of patients included in the Alpha Omega Trial, a randomised controlled trial of omega-3 (n-3) fatty acid supplementation undertaken in 4837 patients aged 60–80 years with a verified history of MI. Patients received state-of-the-art antihypertensive, antithrombotic and lipid-modifying drug treatment, as described in detail elsewhere.<sup>12</sup> The trial started in 2002 and ended in 2009. For this study, patients were selected from whom non-fasting blood was drawn at baseline and after 41 months. Owing to financial constraints, two blood samples were obtained in only 2426 patients (50% of the cohort), i.e. those randomised before August 2005. Of all patients randomised prior to August 2005 ( $n = 2918$ ), 233 patients died during follow-up, 259 patients had missing blood samples or declined to participate, and 16 patients had missing data on BMI and/or waist circumference (WC), yielding an evaluable cohort of 2410 patients (Supplementary Material, Figure S1). The study was conducted in accordance with the Helsinki Declaration and was approved by a central and local medical ethics committee in the Netherlands. Written informed consent was obtained from all patients.

### Body mass index and waist circumference

Body weight and height were measured with the subject wearing light indoor clothing without shoes. BMI was calculated as weight in kilograms divided by the square of height in meters. Following World Health Organization (WHO) guidelines, normal weight was defined as a BMI of 18.5–24.9 kg/m<sup>2</sup>, overweight as a BMI of 25.0–29.9 kg/m<sup>2</sup> and obesity as a BMI of 30.0 kg/m<sup>2</sup> or greater.<sup>1</sup> WC, measured at the midpoint between the bottom rib and the top of the hipbone, was used as a proxy of visceral fat. Men with a WC  $\geq 102$  cm and women with a WC  $\geq 88$  cm were considered to have a high risk of metabolic complications, hereafter referred to as high, as opposed to normal, WC.<sup>1</sup>

### Kidney function assessment

At baseline and after 41 months follow-up we measured from stored blood serum cystatin C (cysC) using a particle-enhanced immunonephelometric assay and serum creatinine (cr) by the modified kinetic Jaffé method, as previously described in detail.<sup>4</sup> We estimated glomerular filtration rate (eGFR) with cysC alone and the combined cr-cysC Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations from 2012, taking into account age, sex and race.<sup>13</sup> In the main analyses, results are shown for eGFR<sub>cysC</sub>, as it is recommended for confirmatory testing in the current Kidney Disease-Improving Global Outcomes (KDIGO) guidelines.<sup>11</sup> In the Supplementary Material the results are presented for eGFR<sub>cr-cysC</sub>. The change (or slope) of the eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub> from baseline to 41 months was calculated for each patient by subtracting the eGFR at baseline from the eGFR after 41 months. Assuming a linear kidney function decline during follow-up, we then calculated an annual decline rate. Rapid kidney function decline was defined as an annual eGFR<sub>cysC</sub> decline of  $\geq 3$  ml/min/1.73 m<sup>2</sup>.<sup>14</sup>

### Data collection

Patients were interviewed and physically examined by trained research nurses at home or in the hospital at baseline and after 41 months. Lipid, glucose and high-sensitivity C-reactive protein (hsCRP) levels were determined as described elsewhere.<sup>15</sup> Information on demographic variables, lifestyle habits, current health status, and medical history were collected by self-administered questionnaires, as previously described.<sup>12</sup> Questionnaires were checked by research nurses. Diabetes mellitus was considered present in the case of a self-reported physician diagnosis, use of glucose-lowering drugs, and/or elevated blood glucose. We used

the average of two blood pressure measurements after a 10-minute seated rest. Medication was coded according to the Anatomical Therapeutic Chemical (ATC) Classification System.

### Data analysis

Baseline characteristics are presented as mean (standard deviation (SD)), median (interquartile range), or number (percentage) as appropriate. Missing data on level of education ( $n=14$ ) were imputed by the sex-specific mode. The relation between BMI or WC and kidney function decline met the linear regression assumptions.

Analysis of covariance (ANCOVA) was used to calculate mean annual eGFR decline rates per WHO category of BMI and for high and normal WC. Normal BMI or normal WC was applied as the reference category. In these analyses, two patients with a BMI  $<18.5 \text{ kg/m}^2$  were excluded. Linear regression was used to study the association between BMI or WC as continuous variables and kidney function decline. Regression coefficients were calculated per  $5 \text{ kg/m}^2$  increment of BMI (approximately one SD), corresponding to the width of each WHO category; and per 10 cm increment of WC, which approximately corresponds to a  $5 \text{ kg/m}^2$  increment of BMI.<sup>16</sup>

The continuous relation between each indicator of body fat (BMI and WC) and kidney function decline was further analysed in a flexible manner using four-knot restricted cubic splines with 95% confidence intervals (CIs). As per general guidelines, the knots were chosen at the 5th, 35th, 65th and 95th percentile of the BMI and WC distribution for men and women separately.<sup>17</sup>

All analyses were adjusted for the n-3 fatty acid treatment groups of the Alpha Omega Trial (three dummy variables). In addition to the treatment group, we adjusted for age at baseline and sex (model 1). According to the WHO, smoking of cigarettes, alcohol consumption and socio-economic status may confound the association of obesity with outcome. Therefore, in model 2 (full model), an additional adjustment was made for these baseline factors: current cigarette smoking (yes, no), alcohol use (yes, no), and level of education (elementary education, low, intermediate and high education) as a proxy for socio-economic status. Analyses were not adjusted for baseline eGFR, since baseline-adjustment in models with change-scores as outcome variable results in biased estimates.<sup>18</sup> In the main analyses we did not control for variables considered likely causal intermediates in the relation between obesity and kidney function decline, such as blood pressure, diabetes, and low-density lipoprotein (LDL)-cholesterol.

Several sensitivity analyses were performed. First, we included factors in the causal pathway, diabetes, systolic blood pressure and LDL-cholesterol, to estimate the presence of mediation. In a separate analysis we controlled for use of renin-angiotensin system (RAS) blocking drugs and physical activity. We explored the presence of effect measure modification between treatment group and BMI or WC with regard to kidney function decline. Finally, we investigated the potential relation between change in BMI or WC from baseline to 41 months follow-up and annual eGFR decline. The main analyses were repeated using eGFR<sub>cr-cysC</sub> decline as outcome. All results are presented for men and women separately, given previously reported differences in kidney function decline between men and women.

Two-sided  $p$ -values  $<0.05$  were considered statistically significant. All analyses were performed using SPSS 23.0 (SPSS, Inc., Chicago, Illinois, USA) and STATA Statistical Software (Statacorp, College Station, Texas, USA), version 14.1.

## Results

### Baseline characteristics

Of all patients, the mean age was 69 years, 79% were men, and 99% were white, median time since MI was 4.0 years. Baseline characteristics according to BMI categories (normal weight, overweight and obesity) are presented in Table 1. Patients with overweight or obesity compared to normal weight had diabetes more often, used blood-pressure-lowering drugs more often, had higher serum cholesterol levels, higher hsCRP levels and lower baseline eGFR<sub>cysC</sub>. A similar trend was observed when comparing low and high WC categories (Supplementary Material, Table S1). Mean (SD) baseline BMI was  $27.5 (3.3) \text{ kg/m}^2$  for men and  $28.4 (4.6) \text{ kg/m}^2$  for women. Mean (SD) WC at baseline was  $102 (9) \text{ cm}$  for men and  $97 (12) \text{ cm}$  for women. Compared to men, women had diabetes more often, used blood-pressure-lowering drugs more often (Supplementary Material, Table S2). BMI and WC were strongly correlated (Pearson correlation coefficient 0.8). Each  $1 \text{ kg/m}^2$  increment of BMI was associated with an additional 2.2 (95% CI: 2.1 to 2.3) cm increment of WC.

### Baseline kidney function

At baseline, mean (SD) eGFR<sub>cysC</sub> was  $83.3 (19.3) \text{ ml/min/1.73 m}^2$  for men and  $74.3 (18.8) \text{ ml/min/1.73 m}^2$  for women. In obese, compared to normal weight, men and women the mean eGFR<sub>cysC</sub> was 81.1 versus  $84.5 \text{ ml/min/1.73 m}^2$  ( $p=0.006$ ), and 69.1 versus  $78.1 \text{ ml/min/1.73 m}^2$  ( $p=0.006$ ).

**Table 1.** Baseline characteristics of 2408 post-myocardial infarction patients, stratified by three categories of weight status according to the World Health Organization (WHO) classification.

	Normal weight (n = 527)	Overweight (n = 1328)	Obese (n = 553)
Age, years	69.3 ± 5.4	69.0 ± 5.4	68.0 ± 5.5
Men, no (%)	419 (79.5)	1116 (84.0)	379 (68.5)
Ethnicity, white, no. (%)	522 (99.1)	1310 (98.6)	548 (99.1)
Higher education, <sup>a</sup> n (%)	77 (14.6)	171 (12.9)	49 (8.9)
Current smoking, no. (%)	106 (20.1)	188 (14.2)	89 (16.1)
Alcohol use, <sup>b</sup> n (%)	388 (73.6)	1004 (75.6)	352 (63.7)
Height, cm	172.5 ± 7.9	173.1 ± 7.8	170.0 ± 8.8
Weight, kg	69.6 ± 7.8	82.0 ± 8.3	94.7 ± 11.7
Body mass index, kg/m <sup>2</sup>	23.3 ± 1.4	27.3 ± 1.4	32.7 ± 2.7
Waist circumference, cm	91.6 ± 7.3	100.9 ± 6.7	111.3 ± 9.2
Physically active, <sup>c</sup> n (%)	119 (22.6)	319 (24.0)	92 (16.6)
Time since myocardial infarction, years	3.6 (1.6–6.1)	4.0 (2.0–6.3)	4.5 (2.4–6.9)
Diabetes, <sup>d</sup> n (%)	65 (12.3)	217 (16.3)	162 (29.3)
Systolic blood pressure, mm Hg	141.3 ± 21.8	144.3 ± 21.4	142.8 ± 20.7
Diastolic blood pressure, mm Hg	79.4 ± 10.6	82.0 ± 10.7	82.0 ± 10.5
Antihypertensive drugs, <sup>e</sup> n (%)	449 (85.2)	1141 (85.9)	505 (91.3)
ACE inhibitors/ATII blockers	265 (50.3)	704 (53.0)	330 (59.7)
Beta blockers	324 (61.5)	863 (65.0)	386 (69.8)
Calcium channel blockers	97 (18.4)	248 (18.7)	117 (21.2)
Diuretics	78 (14.8)	242 (18.2)	177 (32.0)
Glucose-lowering drugs, <sup>f</sup> n (%)	48 (9.1)	159 (12.0)	108 (19.5)
Insulin analogues	11 (2.1)	42 (3.2)	51 (9.2)
Oral glucose-lowering drugs	39 (7.4)	131 (9.9)	81 (14.6)
Lipid-modifying drugs, <sup>g</sup> n (%)	454 (86.1)	1140 (85.8)	480 (86.8)
Statins	452 (85.8)	1129 (85.0)	477 (86.3)
Antithrombotic agents, <sup>h</sup> n (%)	516 (97.9)	1294 (97.4)	541 (97.8)
Total cholesterol, <sup>i</sup> mmol/l	4.78 ± 0.92	4.81 ± 0.94	4.95 ± 0.91
HDL, <sup>i</sup> mmol/l	1.35 ± 0.36	1.25 ± 0.31	1.19 ± 0.31
LDL, <sup>i</sup> mmol/l	2.72 ± 0.79	2.74 ± 0.80	2.77 ± 0.80
Triglycerides, <sup>j</sup> mmol/l	1.41 (1.04–1.91)	1.62 (1.21–2.24)	1.96 (1.51–2.73)
Plasma glucose, <sup>k</sup> mmol/l	5.6 ± 1.7	5.9 ± 1.8	6.6 ± 2.4
High-sensitivity CRP, mg/l	1.24 (0.62–2.73)	1.58 (0.81–3.37)	2.60 (1.11–4.81)
Serum cystatin C, mg/l	0.96 ± 0.23	0.96 ± 0.24	1.00 ± 0.26
Serum creatinine, <sup>l</sup> μmol/l	88.4 ± 26.5	90.2 ± 30.1	91.1 ± 30.9
eGFR <sub>cysC</sub> , <sup>m</sup> ml/min/1.73 m <sup>2</sup>	82.2 ± 19.3	82.3 ± 19.0	78.8 ± 20.9
eGFR <sub>cr-cysC</sub> , <sup>m</sup> ml/min/1.73 m <sup>2</sup>	79.4 ± 18.4	79.2 ± 18.1	76.0 ± 20.0

ACE: angiotensin-converting enzyme; ATII: angiotensin II; ATC: Anatomical Therapeutic Chemical; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; cr: creatinine; CRP: C-reactive protein; cysC: cystatin C; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MET: metabolic equivalent task; SD: standard deviation.

Data are reported as number of patients (%), mean ± SD or median (interquartile range).

Two patients with BMI < 18.5 kg/m<sup>2</sup> were not reported in this table.

<sup>a</sup>Defined as higher vocational education or university.

<sup>b</sup>Defined as ≥ 1 glass per week.

<sup>c</sup>Defined as three or more metabolic equivalent tasks (METs) during ≥ 5 days/week.

<sup>d</sup>Self-reported diagnosis by a physician, use of glucose-lowering drugs, or in case of elevated plasma glucose level (≥ 126 mmol/l in the case of patients who had fasted for four hours or ≥ 200 mmol/l in the case of non-fasting patients).

<sup>e</sup>Blood-pressure-lowering drugs: ATC Classification System codes C02, C03, C07, C08, and C09.

<sup>f</sup>Glucose-lowering drugs: ATC code A10, A10A, A10B, A10X.

<sup>g</sup>Lipid-modifying drugs: ATC code C10, C10AA.

<sup>h</sup>Antithrombotic agents: ATC code B01.

<sup>i</sup>To convert the values for cholesterol to mg/dl, divide by 0.02586.

<sup>j</sup>To convert the values for triglycerides to mg/dl, divide by 0.01129.

<sup>k</sup>To convert the values for glucose to mg/dl, divide by 0.05551.

<sup>l</sup>To convert the values for creatinine to mg/dl, divide by 88.40.

<sup>m</sup>eGFR<sub>cysC</sub> and eGFR<sub>cr-cysC</sub> based on the CKD-EPI equations from 2012.<sup>13</sup>



1.73 m<sup>2</sup> ( $p < 0.001$ ), respectively. Men with a high WC ( $\geq 102$  cm) had a mean eGFR<sub>cysC</sub> of 81.8 ml/min/1.73 m<sup>2</sup> compared to 84.9 ml/min/1.73 m<sup>2</sup> in those with normal WC ( $< 102$  cm) ( $p < 0.001$ ). Women with high WC ( $\geq 88$  cm) and normal WC ( $< 88$  cm) had mean eGFR<sub>cysC</sub> values of 73.6 and 76.8 ml/min/1.73 m<sup>2</sup> ( $p = 0.08$ ).

### Body mass index and kidney function decline

After 41 months of follow-up, mean (95% CI) decline in eGFR<sub>cysC</sub> was  $-4.61$  ( $-5.06$  to  $-4.17$ ) ml/min/1.73 m<sup>2</sup>. Assuming a linear decline in kidney function, this corresponds to an annual decline of  $-1.34$  ml/min/1.73 m<sup>2</sup>. Men and women had an annual eGFR<sub>cysC</sub> decline of  $-1.45$  and  $-0.92$  ml/min/1.73 m<sup>2</sup>, respectively (mean difference 0.53, 95% CI: 0.22 to 0.85). Annual rates

of kidney function decline for normal weight, overweight and obese patients were  $-1.25$ ,  $-1.30$  and  $-1.59$  ml/min/1.73 m<sup>2</sup>, respectively (Table 2). Rapid annual kidney function decline was observed in 25% of obese patients and 23% of normal weight patients ( $p = 0.23$ ). Obese versus normal weight men had an additional annual eGFR<sub>cysC</sub> decline of  $-0.42$  ( $-0.85$  to  $0.02$ ), corresponding to an additional 30% decline in kidney function. Obese versus normal weight women had an additional annual eGFR<sub>cysC</sub> decline  $-0.35$  ( $-1.22$  to  $0.53$ ) ml/min/1.73 m<sup>2</sup>, corresponding to an additional 45% decline in kidney function. Each 5 kg/m<sup>2</sup> increment of BMI was associated with an additional annual eGFR<sub>cysC</sub> decline of  $-0.35$  ml/min/1.73 m<sup>2</sup> in men and  $-0.21$  ml/min/1.73 m<sup>2</sup> in women, corresponding to 25% and 28% of the sex-specific mean annual kidney function decline in normal weight patients

**Table 2.** Mean (95% confidence interval (CI)) annual cystatin C based kidney function decline (ml/min/1.73 m<sup>2</sup>) in 2408 post-myocardial infarction patients according to body mass index (BMI) and waist circumference (WC) category, overall and for men and women separately.

	All patients	Normal weight <sup>a</sup> (ref)	Overweight	Obesity	Normal WC <sup>b</sup> (ref)	High WC
All patients	<i>n</i> = 2408	<i>n</i> = 527	<i>n</i> = 1328	<i>n</i> = 553	<i>n</i> = 1022	<i>n</i> = 1386
Crude	$-1.34$ ( $-1.46$ to $-1.21$ )	$-1.25$ ( $-1.53$ to $-0.98$ )	$-1.33$ ( $-1.50$ to $-1.15$ )	$-1.46$ ( $-1.73$ to $-1.19$ )	$-1.19$ ( $-1.38$ to $-0.99$ )	$-1.45$ ( $-1.62$ to $-1.29$ )
Model 1		$-1.25$ ( $-1.53$ to $-0.98$ )	$-1.29$ ( $-1.47$ to $-1.12$ )	$-1.60$ ( $-1.87$ to $-1.33$ )	$-1.19$ ( $-1.38$ to $-0.99$ )	$-1.57$ ( $-1.75$ to $-1.39$ )
Model 2		$-1.25$ ( $-1.53$ to $-0.98$ )	$-1.30$ ( $-1.48$ to $-1.13$ )	$-1.59$ ( $-1.87$ to $-1.32$ )	$-1.19$ ( $-1.38$ to $-0.99$ )	$-1.57$ ( $-1.74$ to $-1.39$ )
Men	<i>n</i> = 1914	<i>n</i> = 419	<i>n</i> = 1116	<i>n</i> = 379	<i>n</i> = 914	<i>n</i> = 1000
Crude	$-1.45$ ( $-1.59$ to $-1.31$ )	$-1.38$ ( $-1.68$ to $-1.09$ )	$-1.39$ ( $-1.58$ to $-1.21$ )	$-1.69$ ( $-2.00$ to $-1.38$ )	$-1.25$ ( $-1.46$ to $-1.05$ )	$-1.63$ ( $-1.82$ to $-1.44$ )
Model 1		$-1.38$ ( $-1.69$ to $-1.09$ )	$-1.41$ ( $-1.59$ to $-1.22$ )	$-1.82$ ( $-2.14$ to $-1.51$ )	$-1.25$ ( $-1.46$ to $-1.05$ )	$-1.65$ ( $-1.84$ to $-1.45$ )
Model 2		$-1.38$ ( $-1.69$ to $-1.09$ )	$-1.41$ ( $-1.59$ to $-1.23$ )	$-1.80$ ( $-2.12$ to $-1.49$ )	$-1.25$ ( $-1.46$ to $-1.05$ )	$-1.63$ ( $-1.82$ to $-1.44$ )
Women	<i>n</i> = 494	<i>n</i> = 108	<i>n</i> = 212	<i>n</i> = 174	<i>n</i> = 108	<i>n</i> = 386
Crude	$-0.92$ ( $-1.20$ to $-0.63$ )	$-0.75$ ( $-1.42$ to $-0.08$ )	$-0.97$ ( $-1.45$ to $-0.49$ )	$-0.96$ ( $-1.49$ to $-0.43$ )	$-0.61$ ( $-1.28$ to $0.06$ )	$-1.00$ ( $-1.36$ to $-0.65$ )
Model 1		$-0.75$ ( $-1.42$ to $-0.08$ )	$-0.92$ ( $-1.41$ to $-0.44$ )	$-0.94$ ( $-1.47$ to $-0.40$ )	$-0.61$ ( $-1.28$ to $0.06$ )	$-0.95$ ( $-1.32$ to $-0.59$ )
Model 2		$-0.75$ ( $-1.42$ to $-0.08$ )	$-1.03$ ( $-1.54$ to $-0.53$ )	$-1.09$ ( $-1.66$ to $-0.52$ )	$-0.61$ ( $-1.28$ to $0.06$ )	$-1.01$ ( $-1.38$ to $-0.64$ )

Normal weight BMI 18.5–24.9, overweight BMI 25.0–29.9, obesity BMI  $\geq 30.0$  kg/m<sup>2</sup>. Normal and high WC  $< 88$  and  $\geq 88$  cm for women and  $< 102$  and  $\geq 102$  cm for men. Kidney function based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation from 2012.<sup>13</sup> Adjusted variables were fixed at the mean value of the reference group, hence the results of the reference category are equal across models. Two patients with BMI  $< 18.5$  kg/m<sup>2</sup> were not reported in this table.

<sup>a</sup>Reference: annual kidney function decline in normal weight patients.

<sup>b</sup>Reference: annual kidney function decline in normal WC patients.

Model 1: adjusted for treatment group, age and sex (if not stratified for).

Model 2: model 1 plus additional adjustment for current smoking, alcohol use, level of education.

**Table 3.** Association of body mass index (BMI) and waist circumference (WC) with annual cystatin C based kidney function decline in 2410 post-myocardial infarction patients, overall and for men and women separately.

	Additional annual eGFR <sub>cysC</sub> decline, mean (95% CI)		
	Total, n = 2410	Men, n = 1914	Women, n = 496
Per 5 kg/m <sup>2</sup> increment of BMI			
Crude	-0.20 (-0.37 to -0.02)	-0.27 (-0.48 to -0.06)	-0.15 (-0.48 to 0.19)
Model 1	-0.28 (-0.46 to -0.11)	-0.36 (-0.57 to -0.15)	-0.15 (-0.49 to 0.19)
Model 2	-0.28 (-0.46 to -0.10)	-0.35 (-0.56 to -0.14)	-0.21 (-0.55 to 0.14)
Per 10 cm increment of WC			
Crude	-0.24 (-0.36 to -0.11)	-0.19 (-0.35 to -0.04)	-0.19 (-0.46 to 0.08)
Model 1	-0.21 (-0.34 to -0.08)	-0.21 (-0.37 to -0.06)	-0.19 (-0.46 to 0.08)
Model 2	-0.20 (-0.34 to -0.07)	-0.21 (-0.36 to -0.06)	-0.22 (-0.49 to 0.06)

CI: confidence interval; eGFR<sub>cysC</sub>: cystatin C based estimated glomerular filtration rate.

Kidney function based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, 2012.<sup>13</sup>

Model 1: adjusted for treatment group, age and sex (if not stratified for).

Model 2: model 1, additionally adjusted for current smoking, alcohol use, level of education.

(Table 3). Supplementary Material, Table S3 shows the adjusted analysis in more detail. Figure 1(a) depicts the continuous relation between BMI and annual kidney function decline for men and women. There was no effect measure modification between BMI and sex with regard to kidney function decline.

### Waist circumference and kidney function decline

Men and women with high versus normal WC had a faster annual decline in kidney function (Table 2). In men, the additional decline in eGFR (95% CI) was -0.39 (-0.66 to -0.13) ml/min/1.73 m<sup>2</sup>; for women it was -0.40 (-1.17 to 0.36) ml/min/1.73 m<sup>2</sup>. Among patients with high and normal WC, 26% and 21% showed rapid kidney function decline, respectively ( $p=0.003$ ). In regression analysis, a squared WC term was significant in men ( $p=0.03$ ) but not in women ( $p=0.2$ ). For each 10 cm increment of WC there was an additional annual kidney function decline of -0.21 ml/min/1.73 m<sup>2</sup> in men and -0.22 ml/min/1.73 m<sup>2</sup> in women (Table 3 and Supplementary Material, Table S3). Figure 1(b) depicts the continuous relation between WC and annual kidney function decline for men and women.

### Sensitivity analyses

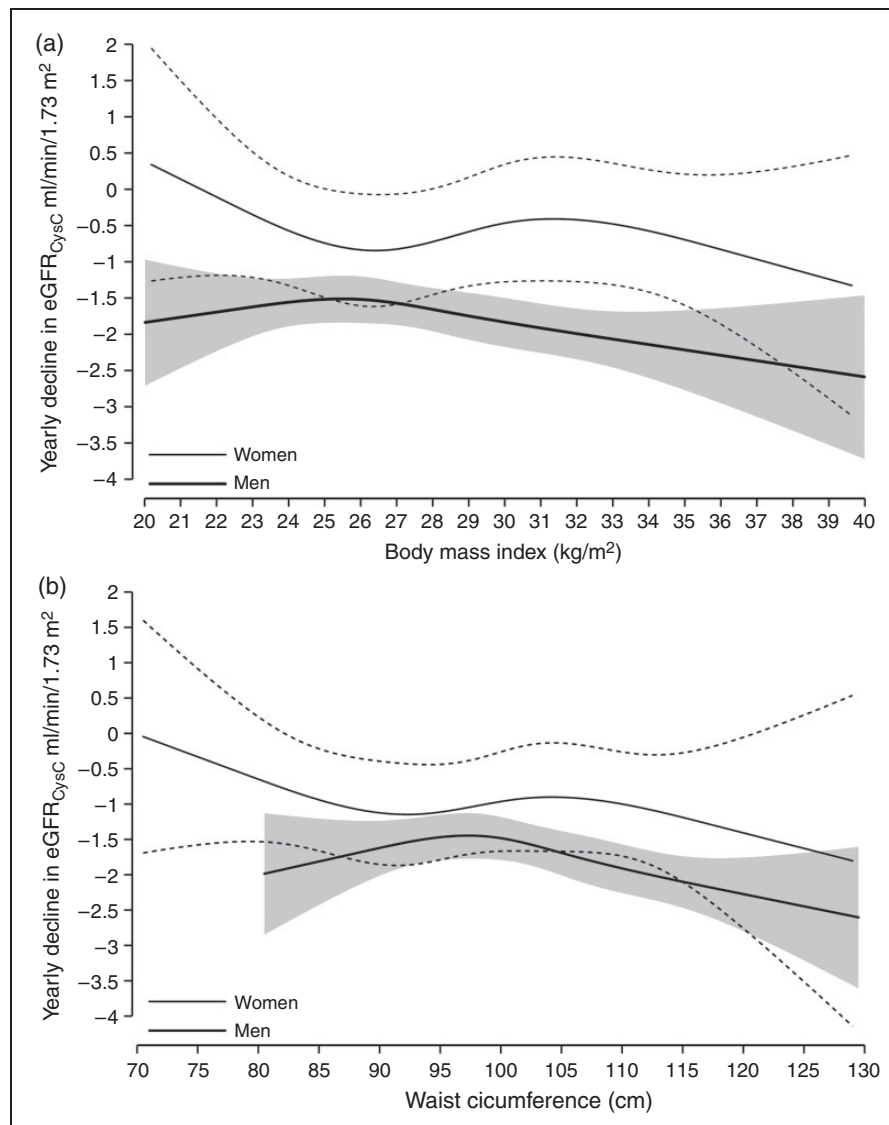
In addition to model 2, further adjustment for diabetes attenuated the association of BMI (and WC) with kidney function decline. The regression coefficient per 5 kg/m<sup>2</sup> BMI changed from -0.28 to -0.20 (Supplementary Material, Table S4). Additional adjustment for systolic blood pressure or LDL-cholesterol did not change the association. Adjustment for use of RAS blocking drugs or physical activity did not essentially

change the results. There was no evidence for effect modification between BMI or WC and treatment group with regard to kidney function decline (data not shown). When WC, instead of BMI, was taken as determinant, results were comparable. On average, BMI and WC did not change during follow-up, with a mean (SD) change of 0.03 (1.67) kg/m<sup>2</sup> and 0.14 (5.99) cm. Change in BMI was not associated with annual eGFR<sub>cysC</sub> decline. The regression coefficient for each unit decline in BMI was -0.052 (-0.129 to 0.024). Likewise, decline in WC was not associated with eGFR<sub>cysC</sub> decline. Finally, taking eGFR<sub>cr-cysC</sub> as the outcome, analysis resulted in slightly weaker effect estimates (Supplementary Material, Tables S5 and S6).

### Discussion

This is the first study to show a progressive association between adiposity and kidney function decline in stable post-MI patients receiving optimal pharmacological treatment. The mean annual decline in kidney function was -1.45 ml/min/1.73 m<sup>2</sup> for men and -0.92 ml/min/1.73 m<sup>2</sup> for women. Obese men and women showed, on average, 30% and 45% faster annual kidney function decline than individuals of normal weight. Each 5 kg/m<sup>2</sup> increment of BMI was associated with an additional annual kidney function decline of -0.35 ml/min/1.73 m<sup>2</sup> in men and -0.21 ml/min/1.73 m<sup>2</sup> in women. Finally, men and women with high versus normal WC experienced a more rapid decline in kidney function.

The annual kidney function decline of -1.3 ml/min/1.73 m<sup>2</sup> observed in our study is lower than the -2.2 ml/min/1.73 m<sup>2</sup> for post-MI patients found in the Prevention of Renal and Vascular End-stage Disease study, possibly because the patients in our



**Figure 1.** (a) Association between body mass index (BMI) and (b) waist circumference (WC) and annual kidney function decline for men and women. Linear regression coefficients for annual kidney function decline according to BMI or WC were modelled by separate restricted cubic splines. Patients with extreme values of BMI ( $<20 \text{ kg/m}^2$  ( $n = 22$ , 0.9%) and  $>40 \text{ kg/m}^2$  ( $n = 11$ , 0.5%)), or WC ( $<70$  for women,  $<80$  for men with BMI  $<20 \text{ kg/m}^2$  ( $n = 2$  and  $n = 1$ ) and  $>130 \text{ cm}$  ( $n = 18$ )) were excluded. The model was adjusted for age, treatment group and current smoking.

eGFR<sub>cysC</sub>: cystatin C based estimated glomerular filtration rate.

cohort received more optimal cardiovascular drug treatment.<sup>5</sup> Other researchers have reported a mean annual eGFR decline of  $-1.0 \text{ ml/min/1.73 m}^2$  in a community-based cohort (mean age 55 years) and  $-1.8 \text{ ml/min/1.73 m}^2$  in healthy individuals (mean age 72 years).<sup>19,20</sup> The size of the association between high BMI and WC on kidney function decline that we found was small. However, a persistently slower kidney function decline may postpone or prevent chronic kidney disease (CKD) in patients at high risk, which is clinically relevant. In addition, we recently showed in the Alpha Omega Cohort Study

a linear increase in mortality risk (cardiovascular and non-cardiovascular) for patients with an eGFR below  $80 \text{ ml/min/1.73 m}^2$ .<sup>4</sup> Preservation of kidney function is therefore important, especially in these high-risk patients.

Few studies have examined the association between BMI and kidney function decline. One study found that in younger healthy adults, being overweight or obese was associated with 1.50 and 1.85 times higher risk of rapid kidney function decline ( $>3\%$  eGFR per year) compared to normal weight individuals.<sup>2</sup> Others have shown that being overweight at a younger age



(26 years), compared to older age (60 years), is associated with double the risk of progression to CKD stage 3–5 by the age of 65.<sup>21</sup> Interestingly, weight loss in obese patients improves kidney function. In morbidly obese patients aged between 18–60 years old with glomerular hyperfiltration, kidney function normalised after weight loss by gastric bypass surgery.<sup>22</sup> We found no association between change in BMI and kidney function decline. However, BMI hardly changed during the relative short follow-up and we had no information whether weight loss was intentional or not. In our study, men had a faster rate of kidney function decline compared to women at each BMI level, but we found no effect modification. In contrast, one meta-analysis found that obese women versus men had a higher risk of CKD compared to normal-weight individuals.<sup>23</sup>

In addition to BMI, we evaluated the effect of WC, since it is a more accurate measure for visceral fat.<sup>1</sup> The correlation coefficient of 0.8 between BMI and WC observed here was similar to that seen in a study which assessed patients with metabolic syndrome (mean age 68 years).<sup>24,25</sup> In line with our results, others reported that individuals with high versus low WC had a 24% versus 20% risk of annual eGFR decline of >5%, in a multi-ethnic non-diabetic population.<sup>25</sup> We found for men an indication of an inverse U-shaped association between WC (or BMI) and eGFR<sub>cysC</sub> decline. A possible explanation is that low weight can be a proxy of underlying disease, which is particularly relevant in elderly patients. However, the wide 95% CIs reflect the great uncertainty for the lower ranges of WC and BMI.

In contrast to our results, some studies have shown that overweight or mild obesity is reno-protective compared to normal weight, both in patients with eGFR < 60 or ≥ 60 ml/min/1.73 m<sup>2</sup>.<sup>9,10</sup> In contrast to our study, this cohort consists of US army veterans (95% men, mean age 73 years), with a lower mean eGFR of 48 ml/min/1.73 m<sup>2</sup>, and a large prevalence of malignancies and lung disease. Moreover, these studies did not control for smoking, which may have contributed to an underestimation of the effect of obesity, while smokers in general have lower BMI.<sup>26</sup>

Various mechanisms have been proposed through which overweight and obesity could promote accelerated loss of kidney function, in addition to diabetic and hypertensive nephropathy. Obesity is associated with a state of low-grade systemic inflammation, and has been shown to cause kidney damage and eventually fibrosis via the activity of pro-inflammatory cytokines such as transforming growth factor  $\beta$ .<sup>27</sup>

This study has limitations. First, the study design is observational, and therefore no causal inferences can be made. Second, we estimated kidney function at only two time points, which reduces precision of the

estimates. Third, we did not measure kidney function directly. However, direct measurement of GFR is cumbersome, expensive, and rarely available in large epidemiological studies, and several reports have suggested that even iothalamate measurement can have daily variations of up to 8%.<sup>28</sup> Fourth, no information was available on proteinuria, an important predictor of kidney function decline. Finally, our results are applicable to post-MI patients and may therefore not be generalisable to other populations. However, both the prevalence of obesity and the prevalence of cardiovascular disease show an increasing trend worldwide, and our cohort of patients therefore represents a growing patient group.

The study has several strengths. First, to our knowledge this is the only large study that explored the association of both BMI and WC with kidney function decline in post-MI-patients receiving optimal pharmacological drug treatment, and for men and women separately. Second, we measured cysC, which is currently the most accurate marker for estimating GFR, and in contrast to the creatinine based eGFR is most likely not affected by glomerular hyperfiltration.<sup>11,29</sup>

In conclusion, we found in older stable post-MI patients that high BMI and WC were associated with progressive cysC-based kidney function decline, despite cardiovascular drug treatment with antihypertensive, cholesterol-lowering, antithrombotic and glucose-lowering drugs. Further research is needed to study whether prevention of obesity or weight loss intervention on-top of cardiovascular drug treatment can slow down the accelerated kidney function decline in post-MI patients.

### Author contribution

KE, JG, EG, DK and EH contributed to conception and design of the manuscript. KE, JG, EG, DK and EH contributed to acquisition, analysis and interpretation, and drafted the manuscript. TS, FD and JF contributed to interpretation. All authors critically revised the manuscript, all gave final approval and all agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship and/or publication of this article: EH is a member of the Guideline Committee of the Dutch Federation of Nephrology. JG

received research funding from Unilever R&D for epidemiological studies of dietary fatty acids and is a member of the Standing Committee on Nutrition of the Dutch Health Council, Working Group on Minerals of the European Food and Safety Authority, and Dutch Academy for Nutritional Sciences, and is a Fellow of the American Heart Association. DK received research funding from the Royal Netherlands Academy of Arts and Sciences and is Member of the Dutch Academy of Nutritional Sciences. KE, TS, JF, FD and EG report that they have no disclosures.

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